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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,298	04/13/2001	Jeffrey R. Dahlen	071959-5301	4762

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EXAMINER	
LAM, ANN Y	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,298	DAHLEN ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-28,32-34 and 38* is/are pending in the application.

4a) Of the above claim(s) *29-31 and 35-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *23-38* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/05,10/05,9/05,11/04, 1/06*
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *3/7/06*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2005 has been entered.

Election/Restrictions

2. This application contains claims directed to the following patentably distinct species:

Species 1) a method for predicting cardiac mortality rate,

Species 2) a method for assigning a prognosis wherein the prognosis is a subsequent myocardial infarction,

Species 3) a method for assigning a prognosis wherein the prognosis is a subsequent onset of angina,

and Species 4) a method for assigning a prognosis wherein the prognosis is a subsequent onset of congestive heart failure.

The species are independent or distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed can have a materially different design, mode of operation, function and effect. In the instant case, the species are mutually exclusive because the prediction or prognosis is different from each other. The inventions with the different predictions or prognosis are not obvious variants because a patient can have any one of those outcomes without having any one of the others. And the inventions as claimed can have a materially different design, mode of operation, function and effect because different markers and/or different levels of markers may be used to carry out those methods.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 27 is generic as to the above species.

3. Upon election of one of the species above, Applicant must further elect a claimed species among the types of first markers as follows.

This application contains claims directed to the following patentably distinct species:

Species 1) CK-MB,

Species 2) C-reactive protein,

and Species 3) the troponins.

The species are independent or distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed can have a materially different design, mode of operation, function and effect. In the instant case, the species are mutually exclusive because the markers are different markers. The inventions, with the different markers, are not obvious variants. And the inventions as claimed can have a materially different design, mode of operation, function and effect because different markers are used.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 23-26 are generic as to the species of markers above.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Barry Wilson on March 13, 2006, a provisional election was made with traverse to prosecute the invention of a method for predicting cardiac mortality rate, claims 23-28, 32-34 and 38, and the troponins. Affirmation of this election must be made by applicant in replying to this Office action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 29-31 and 35-37 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-22 are canceled.

Claims 23-28, 32-34 and 38 are examined below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 23-28, 32-34 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 lines 1-2, recites a "method for predicting cardiac mortality rate in a patient with an acute coronary syndrome". However, the body of the claim does not indicate how the steps allow for prediction of cardiac mortality rate. In other words, it is not clear how cardiac mortality rate is predicted. The limitation "whereby said binding provides a means for determining cardiac mortality rate" is insufficient because it does not indicate how the prediction is made. (Would the mere presence of a marker, i.e., any binding detection, indicate mortality rate? What would the rate be? Would all the markers have to be present? Would the markers have to be above a threshold? What would that threshold be? Or would there just be a comparison between a control? What kind of comparison? What increased level of marker(s) must there be?) For examination purposes, the Office will interpret the preamble to be a method for predicting likelihood of death.

For the same reasons as above, independent claim 25 is vague because it is not clear how the steps allow for prediction of cardiac mortality rate.

Claim 27, lines 1-2, recites a "method for assigning a prognosis to a patient with an acute coronary syndrome" but the claim does not indicate how the prognosis is made. (How is the prognosis assigned? By the mere presence of one marker? Or the mere presence of all the markers? Would the markers have to be above a threshold? What would that threshold be? Or would there just be a comparison between a control? What kind of comparison? What increased level of marker(s) must there be?)

For the same reasons as indicated above, independent claim 33 is vague because it is not clear how the steps allow for assigning a prognosis.

Claims 24, 26, 28, 32, 34 and 38 are rejected under 112, second paragraph because they depend from a claim that is vague as indicated above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 23-28, 32-34 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Newby et al.**, ["Bedside Multimarker Testing for Risk Stratification in Chest Pain Units; The Chest Pain Evaluation by Creatine Kinase-MB, Myoglobin, and Troponin I (Checkmate) Study" Circulaton, (April 10, 2001); 103: pp. 1832-1837], in view of **Antman et al.**, ["Cardiac-specific Troponin I Levels to Predict the Risk of Mortality in Patients with Acute Coronary Syndromes", The New England Journal of

Medicine, (1996), pp. 1342-1349, Vol. 335, No. 18], and further in view of **Richards et al**., ["Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction", Heart, (1999); 81: 114-120].

Newby et al. teach the invention substantially as claimed.

Newby et al. teach that a multimarker strategy that tests for the presence and/or level of a marker of myocardial necrosis is a better method than a single-marker strategy because it identifies more marker-positive patients and earlier than does a single marker strategy (see page 1836, left column, first paragraph). The multimarker strategy, whether it is performed at one point in time or performed as serial testing, is superior than the single marker strategy because it takes into consideration the fact that different markers will be positive at various times and have different sensitivity and specificity (see page 1836, third and fourth paragraphs).

Newby et al. also teach that cardiac troponins are shown to be useful for identifying patients at short-term risk for death in acute myocardial infarction, acute coronary syndromes and general emergency department chest pain populations (see page 1836, second paragraph, first sentence.) The experiments performed by Newby et al. also used cardiac troponin I (see page 1833, left column, in the 2nd paragraph under the heading "Cardiac Markers'; see also page 1835, left column 2nd paragraph.) Moreover, the conclusion made by Newby et al. was that the multimarker strategies performed (i.e., MMS-1 and MMS-2, both of which included cardiac troponin I) indicated that they were the strongest independent predictor of death (see page 1835, left column

second paragraph.) Testing was also performed using blood samples (see page 1833, left col., 5th full paragraph.)

In short, Newby et al. teach that a multimarker strategy is a better method of predicting mortality (see page 1836, left col., 4th paragraph) in a population of patients with acute myocardial infarction or acute coronary syndromes (see page 1836, left col., 2nd paragraph, first sentence). Moreover, Newby et al. specifically teach a multimarker strategy including cardiac troponin I was a strong predictor of death (see page 1835, left col., 2nd paragraph)

Thus, as to independent claims 23, 25, 27 and 33, Newby et al. teach a method for predicting cardiac mortality rate (see page 1836, left col., 4th para.) in a patient with an acute coronary syndrome (see page 1836, left col., 2nd paragraph), comprising drawing a sample of a body fluid from said patient (see page 1835, left col., 2nd paragraph) and testing for cardiac troponin I (see page 1833, left column, in the 2nd paragraph under the heading "Cardiac Markers'; see also page 1835, left column 2nd paragraph.) (As to claims 27 and 33, the prognosis is considered to be cardiac mortality rate, or death.)

However, it is not clear if the method used by Newby et al. to test for the presence and level of troponin I used antibodies. Antman et al. however teach that cardiac troponin I can be measured by immunoassay using antibodies that recognize cardiac troponin I (see page 1343, left column, last paragraph.) Moreover, Antman et al. teach that cardiac troponin I in blood is an independent risk factor that identifies patients presenting with unstable angina or non-Q-wave myocardial infarction who are

at increased risk of death (see page 1347, left col., last paragraph.) Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize antibodies in the Newby et al. method because Antman et al. teach that cardiac troponin I can be detected by immunoassays using known antibodies that bind to cardiac troponin I.

Also, Newby et al. do not teach that a test to predict cardiac mortality rate may include BNP as the second marker. However, Newby et al. do teach that their studies did not depend on or mandate which markers were tested (see page 1836, right column, 3rd full paragraph). Newby et al. also made a general conclusion that multimarker strategies were better than single marker strategies (see page 1836, left column 4th paragraph). Newby et al. also indicated that multimarker strategies are those that incorporate more than 2 cardiac markers (see page 1837, left column, 1st full paragraph).

While Newby et al. fail to teach BNP as a second marker in the method, Richards et al. however provide the motivation to use BNP as an additional marker in the multimarker strategy taught by Newby et al. (or alternatively, as a substitute marker in the multimarker strategy taught by Newby et al.)

Richards et al. teach that plasma BNP measured within 1 to 4 days of acute myocardial infarction is a powerful independent predictor of death over the subsequent 14 months (see page 114, left column, last paragraph under the heading "*Conclusions*"). Richards et al. collected blood samples from patients (see page 114, right col., last paragraph) and tested for cardiac peptides using an immunoassay (i.e., a

binding assay using antibodies), (see page 115, left col., 1st paragraph). The patients in the study had acute myocardial infarction (see table 3 on page 117). Moreover, Richards et al. teach that adding BNP in a multivariate analyses added additional information in predicting the composite end point of death (see page 118, right column, last paragraph). Richards et al. concluded that stratification of patients into low and high risk groups can be greatly facilitated by plasma BNP measurements and that these could be included in the routine clinical work up of patients following myocardial infarction (see page 119, right column, last paragraph, under the heading "CONCLUSION"). While Richards et al. do not specifically state that the same type of analysis, i.e., radioimmunoassay, as used in the experiment may be performed for clinical analyses, it is understood to be the same type, i.e., immunoassay (which uses antibodies). (Alternatively, it would have been obvious to one of ordinary skill in the art that the same type of assay, i.e., immunoassay, used by Richards et al. in the experiment may be used for clinical analyses because Richards et al. teach that BNP can be detected using immunoassays.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide BNP as taught by Richards et al. as an additional marker in the multimarker strategy in the Newby et al. method of predicting cardiac mortality rate in patients with acute myocardial infarction because Richards et al. teach that BNP is a powerful predictor of death in patients with acute myocardial infarction (see page 114, left column, last paragraph under the heading "*Conclusions*") and that adding BNP

as a marker to a multivariate analyses added additional information in predicting death (see page 118, right col., last paragraph).

Richards et al. not only provide a motivation to add BNP as a marker in the multimarker approach of Newby et al. (as just indicated above), but as an alternative, Richards et al., in view of Antman et al., provide a motivation to substitute BNP for myoglobin or CK-MB that was used in the Newby et al. multimarker approach (such that the multimarker approach would include just troponin I and BNP).

More specifically, Richards et al. teach that BNP is a powerful indicator of death in patients with acute myocardial infarction, and Antman et al. teach that cardiac troponin I is an independent risk factor that identifies patients with unstable angina or non-Q-wave myocardial infarction who are at increased risk of death because of the high sensitivity and specificity of this marker (see page 1347, left col., last paragraph). (The Office notes that unstable angina and non-Q-wave myocardial infarction are types of acute coronary syndromes.) It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide BNP and cardiac troponin I in a multimarker approach as taught by Newby et al. because Richards et al. and Antman et al. teach that both BNP and cardiac troponin I are independent factors in predicting mortality in patients with myocardial infarction. (In other words, Richards et al. and Antman et al. suggest that myoglobin and CK-MB, as specifically used in combination with cardiac troponin I in the Newby et al., are not necessary to predict cardiac mortality, and that other combination of markers may be used, such as BNP and cardiac troponin I.)

Thus, with respect to independent claims 23, 25, 27 and 33, Richards et al. teach the steps of contacting a sample with a second antibody (i.e., antibodies used in the radioimmunoassay on page 115, left col., 1st paragraph) that specifically binds to a second marker (BNP), (see page 118, right column, 1st full paragraph);

providing means for determining binding between each of said respective markers and each of said respective antibodies (i.e. the radioimmunoassay, page 115, left col., first paragraph),

whereby said binding provides a means for determining cardiac mortality rate (page 118, right col., last paragraph). (As to claims 27 and 33, the prognosis is considered to be cardiac mortality rate, or death.)

As to the following claims, the references teach the limitations as follows.

As to claims 24, 26, 28,and 34, said body fluid is blood (see Newby et al., page 1833, left column, 4th full paragraph; Antman et al., page 1343, left col., 3rd full paragraph; and Richards et al., page 114, right col., last paragraph).

Regarding the preamble in claims 23 and 27, the above method of predicting cardiac mortality rate is performed on a patient that *has* an acute coronary syndrome (see Newby et al., page 1836, second paragraph, first sentence; see Antman et al., page 1347, left col., last paragraph; and see Richards et al. page 114, left column, last paragraph).

With respect to 32 and 38, the prognosis is considered to be mortality rate or subsequent death (see Newby et al., page 1836, 2nd paragraph, 1st sentence; see

Antman et al., page 1347, left col., last paragraph; and see Richards et al. page 114, left column, last paragraph.)

Regarding the preamble in claims 25 and 33, while the references teach that the markers may be performed on patients *with* acute coronary syndromes, such as acute myocardial infarction (see above with respect to claims 23 and 27), the references however do not specifically state that the patients were actually *diagnosed* with acute coronary syndromes. However, the references suggest that a method of predicting mortality rate using the markers should be performed on those patients who have been diagnosed with acute coronary syndromes because they suggest the benefits of performing such a method on high risk groups (which would include those that actually have been diagnosed with acute coronary syndrome). For example, Newby et al. teaches that routine incorporation of the disclosed multimarker strategy could improve the process of care and minimize costs, and improve outcomes in patients (page 1837, left col., 1st full paragraph). Antman et al. teach that the disclosed method of predicting mortality permits the early identification of patients at increased risk of death (page 1348, right column, last paragraph). Moreover, Richards et al. suggests that stratification of patients into low and high risk groups can be greatly facilitated by plasma BNP measurements and that these could be included in the routine clinical work up of patients following myocardial infarction (see page 119, right column, last paragraph).

Response to Remarks

The Office acknowledges Applicant's remarks indicating that new claims have been added and that they find support throughout the application.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Freitag, 6,171,870, teaches a device for testing blood for the presence of cardiac markers such as troponin I and CK-MB.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on M-Sat 11-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ann Lam

3/12/06